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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,932	07/29/2002	Frank Luyten	522-1783	1230

21559 7590 10/24/2006

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EXAMINER	
WOOD, AMANDA P	
ART UNIT	**PAPER NUMBER**
1657	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,932	LUYTEN ET AL.	
	Examiner	Art Unit	
	Amanda P. Wood	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36,43-45,51 and 55-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36, 43-45, 51, 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendments filed 22 July 2006 have been received and entered.

Claims 31-36, 43-45, 51, and 55-59 have been examined on the merits.

Claim Objections

Claim 31 is objected to because of the following informalities: In line 4, there appears to be a typographical error in the word "comprising." It is unclear whether the dash before "comprising" is meant to delete an extra space or whether it is an error. In line 16, the phrase "to the" should be deleted because it duplicates that in the following line. Appropriate correction is required.

Claim 36 is objected to because of the following informalities: In line 3, the word "co detectable" should be spelled "co-detectable." Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-36, 43-45, 51, and 55-59 stand provisionally rejected on the ground of nonstatutory double patenting over claims 3-15, 27, 30, and 33 of copending Application No. 10/422,475. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method for identifying cells having chondrocyte phenotypic stability comprising assaying the cells for expression of positive and/or negative markers of phenotypic stability, detecting the expression of the markers by sets of DNA probes, and therapeutic compositions comprising cells identified by the claimed assay method.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitation "the formation" in line 12. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "the in vivo formation" in line 14. There is insufficient antecedent basis for this limitation in the claim.

Claim 32 recites the limitation "the formation" in line 12. There is insufficient antecedent basis for this limitation in the claim.

Claim 32 recites the limitation "the in vivo formed cartilage" in line 14. There is insufficient antecedent basis for this limitation in the claim.

It is unclear what Applicant means by the last phrase in claim 32, lines 19-20, "by said isolated or expanded cells in vivo, as evaluated in step e). and/or specific reporter constructs comprising a promoter of said markers," (it is unclear whether Applicant meant to delete the last part of the phrase after the step e) reference, or whether something else is meant by this phrase).

Claim 34 recites the limitation "said set of positive markers" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

In claim 34, Applicant recites the phrase "positive markers in a cells from a cartilage biopsy," in line 3. It is unclear whether Applicant intends to recite a limitation to a cell or to cells plural.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-36, 43-45, 51, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quarto et al in view of by Binette et al (J. of Orthopaedic Research 1998) and Kolettas et al (Journal of Cell Science 1995).

Quarto et al teach a method of determining the expression of positive and negative markers of chondrocyte phenotypic stability comprising the steps of: a) providing a suspension of isolated or expanded chondrocytes and determining a positive or negative marker thereof, b) injecting intramuscularly or subcutaneously in a non-human animal said suspension in an iso-osmotic liquid comprising chondrocytes in an amount equivalent to at least 1×10^6 chondrocytes as applied to nude mice (i.e., immune-deficient mice), c) allowing the formation of cartilaginous tissue, d) sacrificing the animal, e) evaluating the in vivo formed cartilage histologically for stable, non-vascularized cartilage, and f) identifying a positive (i.e., collagen type II) or negative (i.e., collagen type X) molecular marker of the isolated or expanded cells which formed

stable, non-vascularized cartilage in vivo. Quarto et al further teach that the chondrocytes can be obtained from a cartilage biopsy, such as from chick embryo tibiae, a primary culture can be established, and the chondrocytes can then be expanded before injection or transplantation into nude mice either on collagen sponge, hydroxyapatite, or as a cell suspension (see, for example, pg. 4967, col. 1 and 2). In addition, Quarto et al teach that positive markers, such as type I and II collagens (i.e., positive markers co-detectable with BMP-2 or FGFR-3), and negative markers, such as type X collagen (i.e., a negative marker co-detectable with ALK-1), can be detected using antibodies against those markers (see, for example, pg. 4967, col. 1). Furthermore, Quarto et al teach that a graft comprising an expanded population of stable chondrocytes can be implanted into a mammal (i.e., a patient) such as a nude mouse, using devices such as porous hydroxyapatite ceramic tubes or hemostatic sponges (i.e., prosthetic devices) of bovine collagen (see, for example, pg. 4967, col. 2).

Quarto et al do not expressly teach a method wherein cartilage is evaluated histologically to identify the markers collagen type II and collagen type X to determine whether stable, non-vascularized cartilage has formed.

Binette et al teach a method wherein cells released from the digestion of human articular or epiphyseal cartilage were proliferatively expanded and then cultured in suspension. Binette et al teach that the cells were then assayed for markers of the chondrocyte differentiation state (i.e., aggrecan, type-I and type-II collagen). Furthermore, Binette et al teach that since type X collagen is considered a marker of chondrocyte hypertrophy normally not found in stable hyaline articular chondrocytes, the

cells were also assayed for type X collagen to show the extent of chondrocyte differentiation (i.e., show the stability of the cells' phenotype). Binette et al teach that no DNA fragments corresponding to type X collagen mRNA were found in chondrocytes from adult articular cartilage allowed to differentiate for as long as 5 months. In contrast, detectable levels of type X collagen mRNA was found in chondrocytes from the fetal epiphyseal cartilage grown for only 2 weeks in culture. Binette et al teach that adult articular chondrocytes express a stable articular cartilage phenotype (i.e., markers such as collagen II), without evidence of hypertophy (i.e., without evidence of collagen type X) (see, for example, Abstract, pg. 207, col. 2, pg. 208, col. 1-2, pg. 211, col. 1-2, pg. 212, col. 1, pg. 213, col. 2, and pg. 214, col. 1).

Quarto et al do not expressly teach a method wherein mRNA from chondrocytes is hybridized to DNA probes for positive markers for chondrocyte phenotypic stability.

Kolettas et al beneficially teach that chondrocytes obtained from a cartilage biopsy expressed markers at mRNA and protein levels considered characteristic of cartilage (i.e., positive markers and/or markers co-detectable with positive markers) for chondrocyte phenotypic stability), such as types I, II and IX collagens. Furthermore, Kolettas et al beneficially teach a method wherein mRNA from cultured cells was extracted and hybridization performed using labeled cDNA probes for both positive markers (i.e., types I, II and IX collagens) and negative markers, such as type X collagen (see for example, pg. 1992, col. 1 and 2).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Quarto et al based

upon the beneficial teachings provided by Binette et al, with respect to the art-recognized knowledge that collagen type II is a positive marker for articular cartilage phenotypic stability, and the absence, or non-expression, of collagen type X, is also indicative of articular cartilage phenotypic stability, and by Kolettas et al, with respect to the art-recognized method of identifying cells having a particular marker using DNA hybridization, as discussed above. Furthermore, the Quarto et al particularly point out that chondrocytes can be biopsied, cultured, and expanded, then injected or grafted into an animal or patient, and the resulting cartilaginous tissue analyzed for markers indicating chondrocyte phenotypic stability, such as type II collagen (i.e., a marker co-detectable with BMP-2 or FGFR-3), or for markers indicating chondrocyte hypertrophy, such as type X collagen (i.e., a marker co-detectable with ALK-1), and therefore, it would have been obvious and beneficial for the skilled artisan to use the methods taught by Quarto et al so as to determine whether chondrocytes are phenotypically stable, based upon the particular positive and negative markers detected on those cells. In addition, Kolettas et al particularly point out that it is possible to use DNA hybridization to determine whether mRNA of particular markers (i.e., positive and negative markers for chondrocyte phenotypic stability) are present in a population of expanded or isolated chondrocytes. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to develop a therapeutic composition for humans comprising cells identified as phenotypically stable chondrocytes in at least a pharmaceutically acceptable carrier and/or a growth factor, based upon the beneficial teachings of Quarto et al, wherein a composition of

chondrocytes and growth factors was injected into nude mice, and allowed to form cartilage which was subsequently verified histologically as cartilaginous tissue. The result-effective adjustment of particular conventional working conditions (e.g., choosing a particular positive or negative marker to identify, and/or using a particular means of determining the presence of a marker mRNA, such as DNA arrays or chips, Northern hybridization, or RT-PCR) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1657

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PRIMARY EXAMINER